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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/216,641 12/17/98 BURKOTH

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EXAMINER

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HM22/0913

NGUYEN, Q

ART UNIT

PAPER NUMBER

1632

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks**BEST AVAILABLE COPY**

Office Action Summary	Application No.	Applicant(s)
	09/216,641	BURKOTH ET AL.
	Examiner	Art Unit
	Quang Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 26 June 2001.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 1-14 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 15-40 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) Interview Summary (PTO-413) Paper No(s) _____
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

DETAILED ACTION

Applicants' amendment filed on June 27, 2001 in Paper No. 9 has been entered.

Claims 1-40 are pending in the present application. Claims 1-14 are withdrawn from further consideration because they are drawn to the non-elected invention.

Claims 15-40 are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Response to Amendment

The rejection of claim 38 under 35 U.S.C. 102(b) as being anticipated by Sanford et al. (U.S. Patent No. 5,100,792) is withdrawn.

Claim Objections

Claims 25 and 26 are objected to because of the following informalities: the term "using" is not grammatically correct. The term - - by – should be used instead. Appropriate correction is required.

Upon careful reconsideration of the application, following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Claims 15-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method for forming densified particles from a particular pharmaceutical preparation containing a peptide or a protein, comprising pressing or grinding said pharmaceutical preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted preparation into densified particles of suitable size and density for transdermal delivery thereof by needleless injection; the same densified or compacted particular pharmaceutical composition and a unit dosage container for a needleless syringe comprising the same; and a method for transdermal delivering the same to a vertebrate subject;

(2) A method for forming densified particles from a particulate pharmaceutical preparation containing a gene construct, wherein the step of forming densified particles is the step of coating of a gene construct onto ballistic core carriers or encapsulating a gene construct in a microparticle for transdermal delivery thereof by needleless injection; the same densified or compacted particular pharmaceutical composition and a unit dosage container for a needleless syringe comprising the same; and a method for transdermal delivering the same to a vertebrate subject;
does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 15-28 are drawn to a method for forming densified particles from a particulate pharmaceutical preparation, comprising compacting the preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted

preparation into densified particles of suitable size and density for transdermal delivery thereof by needleless injection. Claims 29-37 are directed to a composition of a densified particulate pharmaceutical composition formed from a lyophilized or spray-dried pharmaceutical composition preparation, said densified composition having an average particle size in the range of about 0.1 to 250 μm mean diameter and a particle density in the range of 0.1 to 25 g/cm^3 , whereas claim 39 is directed to a unit-dosage container for a needless syringe comprising the same composition. Claim 40 is directed to a method of delivering a selected pharmaceutical agent to a vertebrate subject, said method comprising providing the same compacted particulate pharmaceutical preparation and delivering to a target tissue or cell of the vertebrate subject by needless syringe.

With regard to the nature of the instant claims, the specification discloses compositions comprising pGREEN-1 or a human growth hormone (hGH) or β -galactosidase expression vector plasmid with trehalose sugar excipient, which were compressed, ground and sieved to form condensed nucleic acid compositions. The compositions were individually administered through a needless injection device to target skin surfaces of either C57BL/10 mice or female pigs. After 24 hours of administration, biopsy samples revealed GFP and β -galactosidase expression in treated sites, whereas hGH expression was not detected. The lack of hGH expression was attributed to the low loading density of the nucleic acid in the composition (See example 2). The specification further teaches the preparation of a densified composition comprising lyophilized recombinant hGH powder (Genotropin), and it demonstrates that

in comparison with the lyophilized rhGH powder, a higher proportion of the densified composition penetrated porcine skin by needleless injection. Additionally, the specification teaches that markedly increased blood serum levels of rhGH were obtained in New Zealand White rabbits that were intradermally administered with densified Genotropin particles through the needleless injection system.

The above evidence has been noted and considered. However, the evidence can not be reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

Regarding to claims 15-20 and 23-28, as written the claims encompass any and all forms of compacting a particulate pharmaceutical preparation that may contain a peptide or protein or a gene construct. With respect to claims encompassing the pharmaceutical preparation of a gene construct, apart from the processes known in the art for encapsulating, coating a gene construct on biolistic core carriers (not contemplated by the instant invention) and pressing the pharmaceutical preparation under high pressure as taught by this application, the instant specification fails to teach any other forms of compacting the particulate pharmaceutical preparation as encompassed by the scope of the claims. As such, it would have required undue experimentation for one skilled in the art to make and use the method as broadly claimed.

With respect to claims encompassing a densified pharmaceutical preparation of a gene construct that is compacted under high pressure to have the recited physical characteristics, when read in light of the specification the sole purpose for the

composition and methods for preparing and using the same is for gene therapy and genetic immunization (See pages 22-24 of the specification). It is unclear whether the gene construct in the densified pharmaceutical preparation of the present invention is still intact and that it is not susceptible to nicks or degradation due to the compacting process under high pressure, specifically at about 1,000 to 24,000 pounds per square inch, such that the pharmaceutical preparation has any beneficial use. A genetic construct in the form of a nucleic acid or DNA molecule is highly sensitive to degradation, particularly for a large genetic construct. This is a particular concern since the instant specification clearly indicates a lack of hGH expression being detected in treated mice or pigs upon administering into said animals a preparation containing an expression plasmid encoding hGH by a needless injection (See example 2). Furthermore, as enablement requires the specification to teach how to make and **use** the claimed invention, the instant specification fails to enable the **use** of the densified particulate pharmaceutical composition comprising a gene construct, and a method of preparing the same for gene therapy and genetic immunization.

Regarding to the gene therapy aspect encompassed by the pharmaceutical scope of the claims, at the effective filing date of the present application, gene therapy was considered to be immature and highly unpredictable (Dang et al., Clin. Cancer Res. 5:471-474, 1999). The instant specification is not enabled for the use of the claimed invention because it fails to provide sufficient guidance for one skilled in the art on the use of the compact or densified particulate pharmaceutical composition comprising of a gene construct of the present invention to obtain any therapeutic effects contemplated

by Applicants. As noted above, it is unclear whether the gene construct in the densified pharmaceutical preparation is intact and that it is not susceptible to nicks or degradation due to the compacting process under high pressure, or during its delivery to a subject by needleless injection. A genetic construct in the form of a nucleic acid or DNA molecule is highly sensitive to degradation, particularly for a large genetic construct. Applicants have noted that known biolistic techniques are not appropriate for use with large DNA molecules since precipitation of such molecules onto core carriers can lead to unstable configurations which will not withstand the shear forces of gene gun delivery (specification, page 7, line 32 continues to line 2 of page 8). Additionally, there is no correlation between the expression of green fluorescent protein (GFP) or β -galactosidase with the desired therapeutic results for treating a plethora of diseases, disorders, genetic defects such as, AIDS, cancer, neurological diseases, cardiovascular diseases, cystic fibrosis, adenosine deaminase deficiency among many others as contemplated by Applicants. There is no evidence of record that the densified pharmaceutical composition comprising a gene construct in the present application could provide any expression of a relevant therapeutic gene product *in vivo* at any level via a needleless injection, let alone a therapeutic expression level. There are several known factors limiting an effective gene therapy, and these include sub-optimal vectors, the lack of a long-term and stable gene expression *in vivo*, as well as the lack of an efficient gene delivery to target tissues (Dang et al., 1999). It is well known in the art that transgene expression *in vivo* is very transient. As examples, Palmer et al. (Proc. Natl. Acad. Sci. 88:1330-1334, 1991) demonstrated that the *in vivo* expression of

human factor IX by transplanted syngeneic recombinant fibroblasts was transient and vanished 1-5 weeks post-transplantation. Riddell et al. (Nature Med. 2:216-223, 1996) reported that five out of six patients seropositive for human immunodeficiency virus developed cytotoxic T-lymphocytes responses specific to a novel protein and eliminated infused autologous CD8+ HIV-specific cytotoxic T cells transduced with a fusion suicide gene (See abstract). Given the lack of guidance or direction provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

With regard to the nucleic acid immunization aspect encompassed by the pharmaceutical scope of the instant claims, the state of the art was also new and unpredictable at the effective filing date of the present application. Chattergoon et al. (FASEB J. 11:753-763, 1997) stated that "Though DNA vaccines have shown promise in animal models and have raised hopes, the technology is considered an emerging technology" (column 1, paragraph 2, page 762). More recently, Leitner et al. (Vaccine 18:765-777, 2000) further stated that "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Leitner et al. also listed several variable factors affecting the immunogenicity of genetic vaccines. These include: the structure of the plasmid backbone, amount of plasmid delivered, expression levels of the antigen, age and strain of the particular species, target tissue, and route of immunization among others (See Table 1, page 767). The instant specification fails to provide sufficient guidance for a skilled artisan on how to

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achieve any therapeutic vaccination using the densified particulate pharmaceutical composition comprising a gene construct of the present invention. As such, it would have required undue experimentation for a skilled artisan to make and use the pharmaceutical composition and the method for preparing the same as claimed.

Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

With respect to claim 40, the claim encompasses the delivery of a compacted particulate pharmaceutical preparation containing a pharmaceutical agent to a target tissue or cell of a vertebrate subject by any and all routes of administration such as intravenous, oral or aerosol deliveries using a needleless syringe. However, apart from the transdermal delivery of the pharmaceutical preparation taught by the present application, the specification fails to provide sufficient guidance for one skilled in the art on how to make and use the method as claimed broadly, especially for achieving therapeutic effects. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so. Moreover, as noted above the physiological art is recognized as unpredictable. Given the lack of guidance provided by the present application, it would

have required undue experimentation for a skilled artisan to make and use the full scope of the method as claimed.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability and current state of the gene therapy, nucleic acid immunization and physiological arts in general, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and **use** the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on June 27, 2001 in Paper No. (pages 8-14) have been fully considered.

Applicants argued that Applicants have provided sufficient detailed disclosure regarding how to make and use the compositions of the present invention. Applicants also argued that the instant claims are not drawn to methods of treating or curing any and all diseases. Additionally, Applicants argued since numerous DNAs for gene therapy or genetic immunization are currently in clinical trials and which are administered to achieve a desired physiological effect, any of these compositions can be converted into a densified composition as taught by the instant application, and one would expect to obtain the same sort of desired effects. Examiner respectfully finds Applicants' arguments to be unpersuasive for the following reasons.

Examiner agrees with Applicants that the instant claims are not directed to methods of treatment or curing any and all diseases. However, the instant claims are

drawn to a method for preparing a densified pharmaceutical composition comprising a gene construct and the same pharmaceutical composition. Since a pharmaceutical composition entails therapeutic effects associated with the composition, there is no evidence of record indicating that a densified pharmaceutical composition comprising a gene construct of the present invention could provide any expression of a relevant therapeutic gene product *in vivo* at any level via a needless injection, let alone a therapeutic expression level to achieve numerous therapeutic effects contemplated by Applicants. Furthermore, as noted above at the effective filing date of the present application, attaining therapeutic effects via gene therapy or genetic immunization remains to be unpredictable. The positive physiological effects observed in the DNAs that are currently used in gene therapy or genetic immunization that Applicants referred to can not be reasonably extrapolated to the contemplated therapeutic effects of the claimed pharmaceutical composition because they differ in compositions and the manner that they are processed.

Accordingly, claims 15-40 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-30, 33-37 and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 15 and its dependent claims 23-28, it is unclear what is encompassed by the phrase "compacting the preparation". Since the phrase is not clearly defined in the specification, for example, by compacting we means, the metes and bounds of the claims can not be clearly determined. The physical or chemical structures utilized in and the active steps involved in compacting the preparation are not defined, and therefore the phrase renders the claims indefinite. Clarification is requested. For the purpose of examination, Examiner interprets the phrase broadly as any means that results the preparation into a compact form.

In claims 15-26, 29-30, 33-37 and 39-40, it is unclear what is encompassed by the phrase "pharmaceutical preparation", and therefore it renders the claims indefinite. The pharmaceutical preparation does not indicate in any way the chemical structure of any essential element or component within said preparation. Also in claim 40, it is unclear if the pharmaceutical preparation contains the selected pharmaceutical agent recited in the preamble of the claim or not. Clarification is requested because the metes and bounds of the claims can not be clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 15-20, 23-27, 29-31, 33-37 and 39-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Bellhouse et al. (U.S. Patent No. 5,630,796).

The claims are drawn to a method for forming densified particles from a particulate pharmaceutical preparation, comprising compacting the preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted preparation into densified particles of suitable size and density for transdermal delivery thereof by needleless injection; a composition of a densified particulate pharmaceutical composition formed from a lyophilized or spray-dried pharmaceutical composition preparation, said densified composition having an average particle size in the range of about 0.1 to 250 μm mean diameter and a particle density in the range of 0.1 to 25 g/cm³; a unit-dosage container for a needless syringe comprising the same composition. Claim 40 is directed to a method of delivering a selected pharmaceutical agent to a vertebrate subject, said method comprising providing the same compacted particulate pharmaceutical preparation of claim 37 and delivering to a target tissue or cell of the vertebrate subject by needless syringe.

Bellhouse et al. teach a method for preparing as well as delivering transdermally into a mammalian subject particles of a powdered therapeutic agent (e.g., protein, analgesics, hormones, drugs such as insulin and calcitonin) that is ground (a form of compacting the powdered therapeutic agent with a pestle and mortar as shown in example 1 of the instant specification) and sieved to a precise diameter (col. 4, lines 13-14 and example 2) using a needless syringe. The particles have a size of between 0.1

and 250 μm , preferably for transdermal powdered drug injection of between 1 and 50 μm , and more preferably between 10 and 20 μm (a typical cell size). Furthermore, the particles have a density in the range between 0.1 and 25 g/cm^3 , for transdermal drug injection, preferably in the range between 0.5 and 2.0 g/cm^3 , and more preferentially 1.0 g/cm^3 (col. 3, line 66 continues to line 8 of col. 4). Additionally, Bellhouse et al. teach that a substantially inert carrier may have to be included to provide the particles with the required size and mass for adequate penetration, particularly if the therapeutic agent is potent or of low density (col. 4, lines 19-22). Bellhouse et al. further disclose that standard currently available techniques such as lyophilisation or free-drying, spray-drying, emulsifying, drying in the presence of trehalose and the like can be used to stabilise an agent, a whole cell for an embodiment of the issued patent, prior to direct injection into the body (col. 2, lines 52-60). Because the pharmaceutical composition disclosed by Bellhouse et al. has the same characteristics such as particle size, particle density suitable for transdermal delivery into a mammalian subject using a needleless injector as those of the present invention, Bellhouse et al. anticipate the instant claimed invention.

Claims 15, 28 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by McElligott et al. (WO 94/23738).

Claims 15 and 28 are drawn to a method for forming densified particles from a particulate pharmaceutical preparation, comprising compacting the preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted

preparation into densified particles of suitable size and density for transdermal delivery thereof by needleless injection; the same wherein the particulate pharmaceutical preparation is a preparation of a gene construct. Claim 38 is directed to particles of a suitable size and density for transdermal delivery by needless injection, consisting of a gene construct and a pharmaceutically acceptable excipient.

McElligott et al. disclose the preparation of a microparticle composition for the controlled release of a nucleic acid to a target cell, the microparticle comprising a nucleic acid conjugated by way of chemical bonds with promoting material which promotes the uptake or the transport to the nucleus or expression of the nucleic acid in the cell, a biocompatible and biodegradable polymeric matrix encapsulating the conjugated nucleic acid (see pages 4 and 5). By interacting with the promoting material and a biocompatible polymeric matrix, the nucleic acid preparation is compacted with respect to free nucleic acid molecules. McElligott et al. further teach that during the preparation of the microparticles, the smaller size of the emulsion droplets can be controlled with increased agitation (page 20, lines 30-31; page 21, lines 12-28). The microparticle ranges in diameter from 1 to 500 microns, suitable for injection, particle bombardment or other methods to cells and tissues either in culture or in the living animal or plant (page 7, lines 9-12). It should be noted that the biocompatible and biodegradable polymeric matrix is a suitable pharmaceutical excipient.

Therefore, McElligott et al. (WO 94/23738) anticipate the instant claims.

Claims 29, 30 and 32-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Bellhouse et al. (U.S. Patent No. 6,010,478).

It is noted for a composition claim, the intended use is not given any patentable weight. Bellhouse et al. teach that particles of a DNA or RNA molecule, are prepared as compositions which can contain one or more added materials such as carriers, vehicles, and/or excipients to increase the amount of solids in particulate compositions for delivering into skin or mucosal tissue using a needleless syringe. Examples of excipients include pharmaceutical grades of dextrose, sucrose, lactose, trehalose, manitol and others (see the entire patent, particularly col. 4, lines 59-64; col. 5, lines 2-15; and col. 10, lines 36-45). Additionally, Bellhouse et al. teach that the particles have an approximate size generally ranging from 0.1 to 250 μm and for gene delivery, the particle size is generally substantially smaller than 10 μm (col. 10, lines 17-23). Furthermore, the particles have densities in the range between about 0.1 and 25 g/cm³ for use in needleless injection (col. 10, lines 32-35).

Therefore, the reference anticipates the instant claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellhouse et al. (U.S. Patent No. 5,630,796) in view of King et al. (U.S. Patent No. 5,486,364) and Gergely et al. (U.S. Patent No. 4,737,366).

The claims are drawn to a method for forming densified particles from a particulate pharmaceutical preparation, comprising compacting the preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted preparation into densified particles of suitable size and density for transdermal delivery thereof by needleless injection; the same method wherein compacting is carried out in a press at about 1,000 to 24,000 pounds per square inch, more preferably wherein compacting is carried out under vacuum.

With respect to the enabled scope of the instant claimed invention, Bellhouse et al. teach a method for preparing as well as delivering transdermally into a mammalian subject particles of a powdered therapeutic agent (e.g., protein, analgesics, hormones, drugs such as insulin and calcitonin) that is ground (a form of compacting the powdered

therapeutic agent with a pestle and mortar as shown in example 1 of the instant specification) and sieved to a precise diameter (col. 4, lines 13-14 and example 2) using a needless syringe. The particles have a size of between 0.1 and 250 μm , preferably for transdermal powdered drug injection of between 1 and 50 μm , and more preferably between 10 and 20 μm (a typical cell size). Furthermore, the particles have a density in the range between 0.1 and 25 g/cm^3 , for transdermal drug injection, preferably in the range between 0.5 and 2.0 g/cm^3 , and more preferentially 1.0 g/cm^3 (col. 3, line 66 continues to line 8 of col. 4). Additionally, Bellhouse et al. teach that a substantially inert carrier may have to be included to provide the particles with the required size and mass for adequate penetration, particularly if the therapeutic agent is potent or of low density (col. 4, lines 19-22). Bellhouse et al. further disclose that standard currently available techniques such as lyophilisation or free-drying, spray-drying, emulsifying, drying in the presence of trehalose and the like can be used to stabilise an agent, a whole cell for an embodiment of the issued patent, prior to direct injection into the body (col. 2, lines 52-60). Bellhouse et al. do not specifically teach compacting a powdered therapeutic agent such as protein, analgesics, hormones, drugs such as insulin and calcitonin in a press at about 1,000 to 24,000 pounds per square inch, and more preferably under vacuum.

King et al. teach a method of making of a pharmaceutical tablet wherein the pharmaceutical active ingredients and excipient are compressed as dry powders of at least 2000 pounds per square inch (See abstract and col. 4, lines 59-67 and col. 5, lines 1-11). Gerger et al. disclose the preparation of a pharmaceutical chewing gum in a

tablet form in which the active substance, filler additives, chewing gum, waxes are mixed in a vacuum mixing vessel and the mixtures are pressed in a tablet press (See abstract and col. 1 line 52 continues to line 9 of col. 2).

Accordingly, at the time of the instant invention it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the method disclosed by Bellhouse et al. by subjecting the powdered therapeutic agent to other forms of compacting, including the compression of the dry therapeutic powder in the presence of an inert carrier under the conditions taught by King et al. and Gerger et al. One of ordinary skilled artisan would have been motivated to carry out the above modification to enhance the mass of a therapeutic agent that is deemed to be of low density by further mixing the therapeutic agent with an inert carrier in order to provide the particles with the required size and mass for adequate transdermal penetration as taught by Bellhouse et al. (col. 4, lines 19-25).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 308-0009.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.


DAVE T. NGUYEN
PRIMARY EXAMINER